Etodolac (Lodine®): Profile of an established selective COX-2 inhibitor

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Abstract—Etodolac was developed in a search for a novel NSAID with an improved efficacy/side effect profile and was launched in the UK in 1985 for the acute and chronic treatment of arthritic conditions. The improved safety profile of etodolac when compared with other NSAIDs posed an anomaly for which there was no explanation at that time. However, the advent of the COX-2 theory served as a possible rationale for etodolac’s improved safety profile, since etodolac has consistently shown selective COX-2 inhibition and COX-1 sparing effects across a wide range of assays. Since first discovery, etodolac has demonstrated a proven track record in a large number of clinical trials in patients with OA and RA extending to 7 years duration and over 14 years of clinical use.

Key words: NSAIDs; etodolac; COX-2.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs used for the treatment of arthritic conditions, are the most commonly prescribed group of drugs world wide. They have been shown to induce their therapeutic effects by decreasing biosynthesis of prostaglandins and other inflammatory agents. Further work in this area has shown that NSAIDs decrease the production of pro-inflammatory prostaglandins by the inhibition of cyclooxygenase (COX). COX exists in two isoforms: the constitutive isoform, COX-1, and the inducible isoform, COX-2. COX-1 is widely expressed and plays a part in homeostatic functions, such as maintaining the integrity of the gastric mucosa, platelet aggregation and regulating gastrointestinal (GI) and renal blood flow. COX-2 has highly restricted expression, although constitutive expression is seen in the kidney and brain, but it is dramatically upregulated at inflammatory sites (Vane et al., 1998). It is postulated that the anti-inflammatory

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efficacy of NSAIDs derives from inhibition of inducible COX-2, whereas the unwanted side effects, such as irritation and ulceration of the stomach lining and renal problems, arise from inhibition of COX-1 (Kawai et al., 1998; Vane et al., 2000). NSAIDs that selectively inhibit COX-2 and have minimal effects on COX-1 might be expected to have high anti-inflammatory efficacy and reduced GI toxicity. Clinical data supports this hypothesis (Kawai et al., 1998; Vane et al., 2000).

2. DEVELOPMENT OF ETODOLAC

Etodolac was developed in a search for novel NSAIDs with an improved efficacy/side effect balance for the acute and chronic treatment of osteo- and rheumatoid arthritis. Etodolac was derived from a new chemical class of NSAIDs, the pyranocarboxylates (Fig. 1). This molecule was selected for clinical development because of its superior therapeutic index between gastric irritation and anti-inflammatory effects in a wide range of pre-clinical tests.

At the time, prostaglandins were recognised as playing an important part in the pathogenesis of pain and inflammation and also in gastric and renal protection (Vane, 1971). The clinical program demonstrated that etodolac effectively inhibited prostaglandin synthesis at sites of inflammation, but appeared not to affect the levels of prostaglandins in the stomach or duodenum. This was clearly demonstrated in a 4-week, double-blind, randomised comparative study of etodolac (600 mg/day) versus naproxen (1000 mg/day) in RA patients published in 1990 (Russell, 1990; Taha et al., 1990). Assays of endoscopic biopsies of gastric and duodenal mucosa revealed that there was no overall suppression of gastric or duodenal prostaglandins in patients receiving etodolac. In contrast, there were marked reductions in gastric and duodenal prostaglandins following treatment with naproxen. A similar study conducted in healthy volunteers has confirmed these observations (Laine et al., 1994).

The improved safety profile of etodolac when compared with routinely used NSAIDs posed an anomaly during its development and early years of clinical use as there was no explanation available at that time. The advent of the COX-2 theory of inflammation served as the possible rationale for etodolac’s improved safety profile.

![Figure 1. Chemical structure of etodolac (1,8-diethyl-1,3,49-tetrahydropyrano-[3,4-b]indole-1-acetic acid).](attachment:image.png)